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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BRANNOCK, MICHAEL T

ART UNIT	PAPER NUMBER
1646	36

DATE MAILED: 03/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 08/954,771	Applicant(s) Ingham, PW
	Examiner Micha l Brannock, Ph.D.	Art Unit 1646

-- Th MAILING DATE of this communication appears n the cov r sh et with the corresp ndenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on Jan 4, 2002

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 123-165 is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 123-165 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 27

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Status of Application: Claims and Amendments

1. Applicant is notified that the amendments put forth in Paper 28 7/30/01, Paper 33 1/3/02 and Paper 35 1/4/02 are have been entered in full.

2. New clams 123-165 are pending.

3. As set forth previously, the claims will be examined only to the extent that they read on *in vitro* methods of modulating neural cells with sonic hedgehog polypeptides, the requirement having been traversed in Paper No. 17, 3/11/00 and Paper No. 24, 1/16/01 and addressed in Paper 26 3/23/01.

It is noted and made of record that Applicants proposed amendments and remarks set forth in Paper 32 (12/17/01) were intended for a related application and not for the instant application, as set forth by Applicant in Paper 33. Therefore, Applicants remarks in Paper 32 will not be considered.

4. The Declaration filed on 12/17/02 under 37 CFR 1.131 has been considered but is ineffective to overcome the rejections based on 35 U.S.C. 112, 1st paragraph. Regarding the issue of the effects of hedgehog proteins in the adult, the previous Office action indicated that the specification provides examples of the use of sonic hedgehog in the promotion of growth, differentiation, and survival of embryonic neuronal cells. It is known that sonic hedgehog is endogenously expressed in embryos, and one of skill in the art would therefore expect that

embryonic tissues would be responsive to sonic hedgehog. However, the specification also discloses experiments that indicate sonic hedgehog is not expressed in adult tissues (see page 110, lines 10-11). One of skill in the art would therefore expect that adult tissues would not be responsive to sonic hedgehog in the same way that embryonic tissues are, or perhaps not responsive at all. The specification has provided no guidance as to the nature of the response of adult tissues to sonic hedgehog. Therefore, one of skill in the art would be required to perform undue trial and error experimentation in order to determine which of the multitude of adult neural cells is responsive to sonic hedgehog, if in fact any exist. Therefore, one skilled in the art would have to undergo an extensive research plan of the type referred to in the Declaration to try to find out which adult neural tissues were amendable to treatment with hedgehog proteins. The specification provides only speculation that certain hedgehog polypeptides could be used in adult tissues but provides the skilled artisan only an invitation to try to find such tissues. The specification provides no practical help in this regard because the specification indicates that sonic hedgehog proteins have not been found to in adult tissues, at all, and that other hedgehog proteins have been found in the adult but only in the liver and the kidney (see page 110). Using this information as a guide, the skilled artisan is basically left to start at point zero, and then to begin to search for adult neural tissues that were amenable to manipulation in any productive way.

Regarding the relevance of the Declaration to the issue of enablement for polypeptides other than sonic hedgehog, the Declaration is unpersuasive. The only data available for a protein

other than sonic hedgehog is that of the Figure of page 2, wherein the data clearly shows that the effect of administration of desert hedgehog was statistically indistinguishable from the effect of administering vehicle alone. Thus, it appears that in the context of treating adult nerve cells, sequence matters.

Sequence Rules Compliance

5. Applicant is notified that the Application appears to be in compliance with the rules regarding sequence disclosures.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 123-165 are provisionally rejected under the judicially created doctrine of double patenting over claims 11-13 of copending Application No. 08/462386. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: *in vitro* methods of promoting the growth, differentiation and/or survival of neuronal cells by contacting the cells with a sonic hedgehog protein.

Applicant's intention (Paper 28) to provide a terminal disclaimer is acknowledged.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 132 and 154 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons:

Claim 154 requires an effective amount of a hedgehog polypeptide, yet the claim does not require that the amount be effective at any particular thing, therefore it is unclear what additional limitations are put on the claim by the presence of the term "effective amount". It is suggested

that the claim be re-worded such that the claim requires that the amount of the polypeptide be effective at promoting survival of neuronal cells, etc.

Claim 154 requires a method to increase the rate of survival of neuronal cells. The term "rate of survival" is confusing because it there is no art-recognized definition of the term and nor is there such a definition of the term provided in the specification. It is suggested that the phrase "increase the survival rate of the neuronal cells" would obviate this term.

Claim 132 requires "the effect of a naturally-occurring hedgehog protein". The claim is indefinite because the specification has not described the effect of a naturally-occurring hedgehog protein and nor is it known in the art what the effects of a naturally occurring hedgehog protein are. It is appreciated in the art that hedgehog proteins are enormously important in embryonic development and the effects of these proteins are extremely complex, and at present, the understanding of the particulars of the effects of hedgehog proteins is in its infancy. Therefore, the skilled artisan would not be able to unambiguously say what is and what is not "the effect of a naturally-occurring hedgehog protein".

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 123-165 are rejected under 35 U.S.C. 112, first paragraph, as set forth previously in item 13 of Paper 36, because the specification, while being enabling for methods of promoting growth, differentiation and/or survival of embryonic neuronal cells by administering a polypeptide (sonic hedgehog) of SEQ ID NO: 8, 11, 12, and 13 or an N-terminal autoproteolytic portion thereof (as described in the specification), does not reasonably provide enablement for administering a polypeptide other than a polypeptide of SEQ ID NO: 8, 11, 12, and 13, nor for the administration of portions of the polypeptides other than that of the N-terminal autoproteolytic portion, and nor does the specification provide enablement for promoting growth, differentiation and/or survival of neuronal cells other than embryonic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims, for the reasons set forth previously and reiterated below:

The claims encompass methods of promoting one or more of growth, differentiation and survival of adult neuronal cells in culture. The specification provides that neuronal cells grown in culture, including those from adult tissue, readily lose their differentiated state (see page 59, line 18). Also, the specification puts forth that hedgehog proteins can be added to cultures of cells in order to maintain the integrity of a culture of terminally differentiated neuronal cells by preventing loss of differentiation (see page 59, lines 22-25). Additionally, the specification provides examples of the use of sonic hedgehog in the promotion of growth, differentiation, and survival of embryonic neuronal cells. It is known that sonic hedgehog is endogenously expressed

in embryos, and one of skill in the art would therefore expect that embryonic tissues would be responsive to sonic hedgehog. However, the specification also discloses experiments that indicate sonic hedgehog is not expressed in adult tissues (see page 110, lines 10-11). One of skill in the art would therefore expect that adult tissues would not be responsive to sonic hedgehog in the same way that embryonic tissues are, or perhaps not responsive at all. The specification has provided no guidance as to the nature of the response of adult tissues to sonic hedgehog. Therefore, one of skill in the art would be required to perform undue trial and error experimentation in order to determine which of the multitude of adult neural cells is responsive to sonic hedgehog, if in fact any exist.

Applicant argues that several post-filing date references have indicated that certain hedgehog proteins have been detected in several adult neural tissues and that mutations in Dhh apparently cause nerve abnormalities. This argument has been fully considered but not deemed persuasive. It is this type of research (reported in the references applicant cites) that is required by one highly skilled in the art to just begin to determine which neural cell types might be amenable to treatment with hedgehog polypeptides, and then to try to determine which particular hedgehog polypeptides could be used for a particular treatment, and then to try to find a particular technique to use to administer the particular hedgehog polypeptides to treat the particular adult tissues. The instant specification has only provided an invitation to the skilled artisan to begin this extensive and unduly burdensome research plan.

Additionally, the claims encompass an almost limitless number of polypeptides that comprise a portion of SEQ ID NO: 8, 11, 12, 13, 14, 15, 16, 17, 20 or 21 or comprise variants or portions of variants having a recited degree of identity to SEQ ID NO: 8, 11, 12, 13, 14, 15, 16, 17, 20 or 21. Also, it should be pointed-out that SEQ ID NO: 20 and 21 are small nucleic acid sequences according to the sequence listing. Additionally, SEQ ID NO: 15, 16 and 17 appear to be only fragments of an unidentified fish protein. The specification sets forth that variants and portions can be used in the claimed methods, however, the specification does not provide sufficient guidance as to which of these variants and portions can actually be used to practice the claimed invention (see page 26 for example).

One of skill in the art is left to extensive experimentation wherein amino acids are randomly changed, deleted, or added to a polypeptide of SEQ ID NO: 8, 9, 12, or 13, and through trial and error experimentation is left to determine when a polypeptide is obtained that could used to promote neural cell growth, differentiation and/or survival. Such extensive random trial and error experimentation is considered undue.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or

regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active variants or portions that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

Applicant argues that the specification provides extensive guidance that would permit the skilled artisan to prepare many variant sequences, e.g. several alignments and consensus sequences useful for gauging the amenability of a particular amino acid substitution are provided.

Applicant further urges that "Mother Nature herself has performed the background research that would make such experimentation undue. By demonstrating which residues are conserved and which are variable throughout diverse organisms such as mice, humans, etc., Applicants have provided ample guidance to allow the rapid identification by one of skill in the art of suitable variants and fragments of the sequences disclosed".

This argument has been fully considered but not deemed persuasive. It is well established in the art that homology comparisons of the kind described by Applicant cannot be relied upon to predict the effect of amino acid substitution. Bowie et al. directly address Applicant's assertions at col 1, last paragraph of page 1308: "Functionally important residues should be conserved in sets of active sequences, but it is not possible to decide whether a side chain is functionally or structurally important just because it is invariant or conserved. To make this distinction requires an independent assay of protein folding".

Applicant argues that the previous Office action implicitly suggests that only sonic hedgehog sequences would be expected to be active in the claimed methods, but fails to provide facts or reasoning. This argument has been fully considered but not deemed persuasive. Applicant's assertion is incorrect. The prior Office action simply asserted that the specification has not taught how to identify other polypeptides without undue experimentation.

Applicant argues that Chang et al. teach that a mouse sonic hedgehog protein can function in drosophila in a manner similar to the native hedgehog. Thus Applicant argues that the specification is enabled for the full scope of the claims. This argument has been fully considered

but not deemed persuasive. It should be pointed out that the mouse hedgehog used by Chang et al. is a naturally occurring sonic hedgehog protein that has been indicated above as being enabled. More to the point, it is this type of research and investigation that is required to determine which polypeptides are amenable to which applications. The figure on page 2 of EXHIBIT B of Applicant's Declaration, Paper 31, demonstrates that only sonic hedgehog and not desert hedgehog was capable of improving recovery after sciatic nerve crush, e.g. it appears that the effect of desert hedgehog was not significantly different from vehicle alone. Thus, to use the invention commensurate in scope with that as claimed requires further experimentation of the type of Chang et al. and of that described in the Applicants' Declaration in order to determine which polypeptides (of the limitless number claimed) can be used to practice the claimed invention in any particular of the practically limitless number of ways it is claimed to be used.

Therefore, due to the large quantity of experimentation necessary to generate the almost limitless number of variants and portions required by the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Fridays from 8:00 a.m. to 4:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

March 23, 2002

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
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